Tandem Reaction of Ethyl α-(Per(poly)fluoroalkyl)acetates with Allylic Alcohols: A Convenient Synthesis of Ethyl α-(2-Alkenyl)-α-(per(poly)-fluoroacyl)acetates

Bing-Hao Luo, Hui-Ping Guan, and Chang-Ming Hu*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Received October 31, 1996

Fluoroorganic derivatives can be considered to be xenobiotic substances due to the rarity of naturally occurring organofluorine compounds.[1] Also, it is well known that the regio- and stereospecific introduction of fluorine atom(s) into an organic molecule might alter its biological and physical properties profoundly. Therefore, the synthesis of organofluorine compounds has become increasingly important in the medical, agrochemical, and new material field,[2] while the fluorine-containing building-block strategy has now become one of the most convenient approaches in this respect.

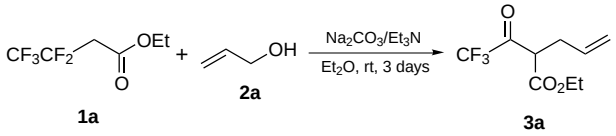
A tandem reaction, the combination of two or more reactions whose occurrence is in a specific order,[3] can not only simplify a multistep synthesis, but also lead to interesting and novel molecules.[4] Herein, we report a tandem reaction of ethyl α-(per(poly)fluoroalkyl)acetates with allylic alcohols in the presence of a mixed base to afford ethyl α-(2-alkenyl)-α-(per(poly)fluoroacyl)acetates (**3**) (Scheme 1). These products, which are valuable starting materials in the synthesis of fluorine-containing heterocyclic compounds,[5] could not be conveniently prepared by direct alkylation of *β*-keto esters.[6]

Results and Discussion

Recently, we found that ethyl α-(per(poly)fluoroalkyl)acetates (**1**), which are available through the sodium dithionite-initiated addition reaction of per(poly)fluoroalkyl iodides (R_fI) to ethyl vinyl ether followed by oxidation and esterification,[7] are versatile synthetic intermediates for the preparation of heterocyclic derivatives.[8]

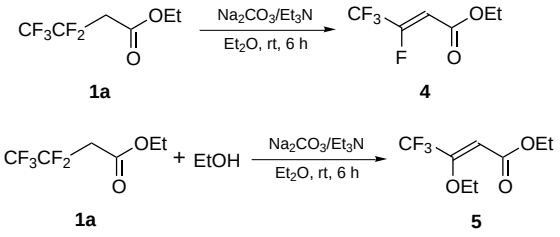
With sodium carbonate and triethylamine as a mixed base, ethyl 3,3,4,4,4-pentafluorobutyrate (**1a**) gave the dehydrofluorination product **4** in ether,[9] and in the presence of ethanol, ethyl 3-ethoxy-4,4,4-trifluorocrotonate (**5**) was obtained in high yield at ambient temperature (Scheme 2).

Scheme 1



1a **2a** **3a**

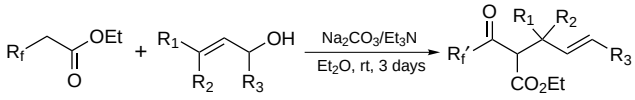
Scheme 2



1a **4**

1a **5**

Scheme 3



1a–g **2a–f** **3a–o**

However, compound **3a** was formed when **1a** (or **1a′**) was treated with allyl alcohol **2a** under basic conditions. The structure of **3a** was determined by spectral and analytical data. The IR sprectrum showed two carbonyl absorptions at 1772 and 1712 cm^{-1}. The ^{19}F NMR spectrum revealed that the fluoroalkyl group of the product contained one less carbon than that of the starting material. Ester **1a** also reacted with various allylic alcohols (**2a**−**f**) to give ethyl 2-(2-alkenyl)-4,4,4-trifluoroacetoacetates (**3a**−**f**) in good yields. Other α-(per(poly)fluoroalkyl)acetates (**1a**−**g**) also reacted with allylic alcohols to give the same results (Scheme 3). The chain length of the fluoroalkyl groups and the presence of *ω*-chlorine or *ω*-bromine in the fluoroalkyl groups showed little effect on the reaction. The reaction proceeded smoothly in dipolar aprotic solvents such as diethyl ether, dichloromethane, tetrahydrofuran, 1,4-dioxane, etc. but gave complicated results when the reaction temperature was raised. The results are shown in Table 1.

Based on the fact that ethyl 3,3,4,4,4-pentafluorobutyrate (**1a**) reacted with ethanol to afford ethyl 3-ethoxy-4,4,4-trifluorocrotonate (**5**), the following reaction pathway is proposed. First, **1a** gave the dehydrofluorination intermediate **4** in the presence of the mixed base. The nucleophilic allyl alcoholate attacked **4** and then underwent dehydrofluorination to give the compound **6**, which afforded the final product **3a** through a Claisen rearrangement. Thus, a tandem reaction sequence of three successive steps was performed (Scheme 4).

In summary, an efficient synthesis of ethyl α-(2-alkenyl)-α-(per(poly)fluoroacyl)acetates was presented. These compounds, bearing a rather reactive 1,3-dicarbonyl group and a carbon−carbon double bond, are useful building blocks in the synthesis of organofluorine derivatives. The simplicity of the experimental procedure, the

* To whom correspondence should be addressed. Fax: 086-21-64166128.

(1) Resnati, G. *Tetrahedron* **1993**, *49*(42), 9385. Meyer, M.; O'Hagan, D. *Chem. Br.* **1992**, *28*, 785. Harper, D. B.; Hamilton, J. T. G.; and O'Hagan, D. *Tetrahedron Lett.* **1990**, *31*(52), 7661.

(2) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha: Tokyo, 1982. Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Ellis Horwood: New York, 1976.

(3) Ho, T. L. *Tandem Organic Reaction*; John Wiley and Sons: New York, 1992.

(4) Mal, D.; Hazra, N. K. *Chem. Commun.* **1996**, 1181. Bunce, R. A. *Tetrahedron* **1995**, *59*(48),13103. Teitze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 131.

(5) Begue, J. P.; Bonner-Delpon, D.; Dogbeavor R.; Ourevitch, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2787. Antonioletti, R.; Cecchini, C.; Ciani, B.; Magnanti, S. *Tetrahedron Lett.* **1995**, *36*(49), 9019. Antonioletti, R.; Bonadies, F.; Scettri, A. *Tetrahedron Lett.* **1988**, *29*(39), 4987.

(6) Shimuzu, I.; Toyoda, M.; Terashima, T.; Oshima, M.; Hasegawa, H. *Synlett*, **1992**, 301. Aubert, C.; Begue, J. P.; Charpentier-Morize, M.; Nee, G.; Langlois, B.; Nee, G. *J. Fluorine Chem.* **1989**, *44*, 377. Begue, J. P.; Charpentier-Morize, M.; Nee, G. *J. Chem. Soc., Chem. Commun.* **1989**, 83.

(7) Huang, W. Y.; Lu, L. *Chin. J. Chem.* **1991**, 167.

(8) Hu, Q. S.; Guan, H. P.; Hu, C. M. *J. Fluorine Chem.* **1995**, 75, 51. Guan, H. P.; Hu, C. M. *Chin. J. Chem.* **1996**, 1, 87. Guan, H. P.; Hu, C. M. *Synthesis* **1997**, in press.

(9) Hu, Q. S.; Hu, C. M. *J. Fluorine Chem.*, in press.

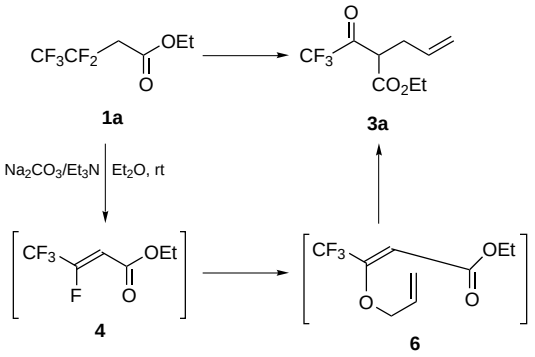
S0022-3263(96)02036-1 CCC: $14.00

Table 1. Reaction of Esters 1 with Allyl Alcohols 2

					allylic alcohol				
entry	esters **1**	R_f	R_f'		R_1	R_2	R_3	product **3**[a]	yield[b] (%)
1	**1a**	CF_3CF_2	CF_3	**2a**	H	H	H	**3a**	75
2	**1a′**	CF_3CFBr	CF_3	**2a**	H	H	H	**3a**	82
3	**1a**	CF_3CF_2	CF_3	**2b**	CH_3	H	H	**3b**	86
4	**1a**	CF_3CF_2	CF_3	**2c**	C_3H_7	H	H	**3c**	85
5	**1a**	CF_3CF_2	CF_3	**2d**	CH_3	CH_3	H	**3d**	85
6	**1a**	CF_3CF_2	CF_3	**2e**	CH_3	H	$CH_2C{\equiv}CH$	**3e**	78
7	**1a**	CF_3CF_2	CF_3	**2f**	Ph	H	H	**3f**	82
8	**1b**	$CF_3(CF_2)_3$	$CF_3(CF_2)_2$	**2a**	H	H	H	**3g**	80
9	**1c**	$CF_2(CF_2)_5$	$CF_3(CF_2)_4$	**2a**	H	H	H	**3h**	86
10	**1d**	$Cl(CF_2)_2$	$ClCF_2$	**2a**	H	H	H	**3i**	78
11	**1e**	$Cl(CF_2)_4$	$Cl(CF_2)_3$	**2a**	H	H	H	**3j**	85
12	**1f**	$Cl(CF_2)_6$	$Cl(CF_2)_5$	**2a**	H	H	H	**3k**	82
13	**1g**	$Br(CF_2)_2$	$BrCF_2$	**2a**	H	H	H	**3l**	79
14	**1e**	$Cl(CF_2)_4$	$Cl(CF_2)_3$	**2f**	Ph	H	H	**3m**	80
15	**1f**	$Cl(CF_2)_6$	$Cl(CF_2)_5$	**2f**	Ph	H	H	**3n**	78
16	**1g**	$Br(CF_2)_2$	$BrCF_2$	**2f**	Ph	H	H	**3o**	84

[a] Satisfactory spectral data were obtained for all compounds. [b] Isolated yield, based on **1**.

Scheme 4



ready availability of the reagents, and the high yields enable this route to be a practical approach.

Experimental Section

The ^1H NMR spectra were measured with $CDCl_3$ as the solvent and TMS as the internal standard. The ^{19}F NMR were measured with CF_3COOH as the external standard and with positive upfield shifts.

General Procedure. To an ether (10 mL) solution of 4 mmol of **1** and 10 mmol of **2** were added sodium carbonate (12 mmol) and triethylamine (1 mL). The mixture was stirred at room temperature for 3 days and then diluted with water (40 mL) and extracted with ether. The combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel to give **3** in good yield.

Ethyl 4,4,4-trifluoro-2-(1-methyl-2-propenyl)-3-oxobutanoate (3b): IR ν_{max} (cm^{-1}) 3088, 2985, 1774, 1743, 1645, 1261, 1212, 1156; ^1H NMR δ 5.65 (1H, m), 5.12 (1H, d, J = 5 Hz), 4.99 (1H, s), 4.20 (2H, q, J = 7 Hz), 3.78 (1H, d, J = 9 Hz), 3.05 (1H, m), 1.29 (3H, t, J = 7 Hz), 1.21 (3H, d, J = 10 Hz); ^{19}F NMR δ 1.1 (s); MS (*m*/*e*) 239 ($M^+ + 1$, 6.68), 223 (15.36), 211 (3.58), 193 (9.04), 165 (31.98), 141 (83.37), 117 (22.23), 55 (100). Anal. Calcd for $C_{10}H_{13}F_3O_3$: C, 50.42; H, 5.46; F, 23.95. Found: C, 50.26; H, 5.52; F, 23.78.

Ethyl 4,4,4-trifluoro-2-(1-propyl-2-propenyl)-3-oxobutanoate (3c): IR ν_{max} (cm^{-1}) 3084, 2964, 1774, 1743, 1644, 1211, 1156; ^1H NMR δ 5.60 (1H, m), 5.17 (1H, d, J = 5 Hz), 5.04 (1H, s), 4.17 (2H, q, J = 7 Hz), 3.85 (1H, m), 2.95 (1H, m), 1.30 (4H, m), 1.25 (3H, t, J = 7 Hz), 0.91 (3H, t, J = 5 Hz); ^{19}F NMR δ 1.2 (s); MS (*m*/*e*) 267 ($M^+ + 1$, 9.68), 265 (5.94), 237 (4.40), 223 (39.60), 195 (24.80), 169 (56.46), 141 (54.39), 127 (42.03), 83 (100). Anal. Calcd for $C_{12}H_{17}F_3O_3$: C, 54.14; H, 6.39; F, 21.43. Found: C, 53.98; H, 6.38; F, 22.16.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 29632003) for financial support.

Supporting Information Available: Spectral data for compounds **3a** and **3d**−**3o** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9620369